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Fluid Resuscitation Dilemma in End-stage Renal Disease Patients Presenting with Sepsis: A Systematic Review and Meta-analysis

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Abstract

Background: This study aims to investigate the safety and efficacy of guideline-directed fluid resuscitation (GDFR) compared with conservative fluid management in end-stage renal disease (ESRD) patients with sepsis by evaluating 90-day mortality and intubation rate. **Methods:** Following PRISMA guidelines, a systematic review was conducted across multiple databases using specific keywords and controlled vocabulary. The search strategy, implemented until October 1, 2023, aimed to identify studies examining fluid resuscitation in ESRD patients with sepsis. The review process was streamlined using Covidence software. A fourth reviewer resolved discrepancies in study inclusion. A random-effects model with the generic Mantel–Haenszel method was preferred for integrating odds ratios (ORs). Sensitivity analysis and publication bias analysis were performed. **Results:** Of the 1274 identified studies, 10 were selected for inclusion, examining 1184 patients, 593 of whom received GDFR. Four studies were selected to investigate the intubation rate, including 304 patients. No significant mortality or intubation rate difference was spotted between both groups [OR = 1.23; confidence interval (CI) = 0.92-1.65; $I^2 = 0\%$ and OR = 1.91; CI = 0.91-4.04]. In most studies, sensitivity analysis using the leave-one-out approach revealed higher mortality and intubation rates. The Egger test results indicated no statistically significant publication bias across the included studies. **Conclusion:** Our research contradicts the common assumption about the effectiveness of GDFR for sepsis patients with ESRD. It suggests that this approach, while not superior to the conservative strategy, may potentially be harmful.

Keywords

end-stage kidney disease, sepsis, septic shock, fluid resuscitation, meta-analysis

Introduction

Sepsis is a potentially life-threatening condition characterized by the body's disproportionate response to an infection.[1] This overwhelming systemic response can compromise hemodynamic stability, primarily due to its harmful effects on vascular tone and permeability.[2] Intravenous fluid resuscitation is pivotal in managing sepsis as it helps restore the effective circulating volume, thereby optimizing tissue perfusion and oxygen delivery. Therefore, current guidelines strongly recommend the rapid initiation of intravenous fluid resuscitation in septic patients, known as guideline-directed fluid resuscitation (GDFR).[3] Specifically, an initial bolus of 30 mL/kg is often advocated for patients presenting with sepsis and signs of hypoperfusion.[3]

However, the guidelines for sepsis might only apply to some patients. For instance, studies demonstrated that patients with preexisting end-stage renal disease (ESRD), congestive heart failure, and obesity are less likely to achieve adequate fluid resuscitation with 30 mL/kg due to the perceived risk of volume overload and deleterious outcomes.[45–6] Therefore, physicians opt for conservative fluid resuscitation strategies for these patients to prevent such complications. ESRD patients on hemodialysis have a unique fluid resuscitation tolerance.

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In the US, infection is the second leading cause of mortality in these patients, with sepsis present in over 75% of cases due to repetitive exposure to pathogens during hemodialysis, altered fluid and electrolyte balance, and compromised renal function. This makes sepsis management more challenging.[78–9]

Building upon the challenges posed by sepsis in ESRD patients, we conducted a systematic review and meta-analysis to identify the best practices for fluid management in ESRD patients with sepsis. We compared study outcomes such as mortality and intubation rates in patients who received either GDFR or liberal (≥30 mL/kg) fluid resuscitation or limited or restrictive (<30 mL/kg) fluid resuscitation. Our hypothesis is that GDFR may not benefit ESRD patients with sepsis.

Methods and Statistical Analysis

Search strategy Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting guidelines were followed in this systematic review, and it was conducted strictly by the protocol registered in the PROSPERO (CRD42023475893).

The search was conducted using PubMed, Cochrane Library, and Embase with a controlled vocabulary (Medical Subject Headings) and keywords. Additionally, we reviewed relevant references from the included studies and conference proceedings. Date and language restrictions were not applied. The last search update was performed on October 1, 2023.

We utilized a controlled vocabulary including Medical Subject Headings (MeSH) and keyword searches to thoroughly capture relevant studies using the following search strings combination ((“Renal Insufficiency, Chronic”[Mesh] OR “End Stage Renal Disease”[Mesh] OR ESRD) AND “Sepsis”[Mesh] OR “Septicemia”[Mesh] OR “Bacterial Infections and Mycoses” [Mesh]) AND (“Fluid Therapy”[Mesh] OR “fluid resuscitation” OR “hydration therapy”[Mesh] OR “Fluid Management”[Mesh] OR “Fluid Overload”[Mesh])). The connectors/Boolean operators used were “AND” and “OR.”

The control group and outcomes were not defined in search terms to maximize the scope of relevant articles. Research and review articles were hand searched for pertinent further trials and subgroup analyses. Reviewers used Covidence software to store search results, identify duplicates, and track screening decisions. Three reviewers (NP, JK, and GK) independently screened the titles and abstracts and then reviewed full-text records to assess eligibility for data extraction. A fourth reviewer (KG) resolved disagreements regarding inclusion.

The inclusion criteria for the systematic review and meta-analysis were the following:

1. Population: ESRD adult patients (>18 years of age) presenting with sepsis.
2. Outcomes: 90-day mortality and intubation rate.
3. Comparator: Patients that received <30 mL/kg of IV fluids.
4. Intervention: Patients that received ≥30 mL/kg of IV fluids.
5. Study design: Retrospective or prospective cohort, randomized controlled clinical trials, and case-control studies were included.

Studies were excluded based on several factors: studies not involving adult populations (age < 18), nonpeer-reviewed articles, and studies not reporting specific outcomes of interest, such as 90-day mortality and intubation rates. We also excluded studies with incomplete data, those that did not use a controlled intervention and comparison, and those whose primary focus was not on ESRD patients with sepsis (Figure 1).

Extraction was done through 2 iterations, the second ensuring the fidelity of the first. Data synthesis for the meta-analysis was performed using Review Manager version 5.4 (The Cochrane Collaboration). Data on dichotomous outcomes was presented as risk ratio [odds ratio (OR)], 95% confidence intervals (CIs), and P values. A random-effects model with the generic Mantel–Haenszel method was preferred for integrating ORs. All P values were 2-tailed and were considered statistically significant if <.05. The I^2 method was used to assess the magnitude of variation secondary to heterogeneity. Heterogeneity between studies was evaluated graphically as a forest plot plus the I^2 statistic, whereby $I^2 = 0\%$ indicates minimal heterogeneity, $0\% < I^2 < 30\%$ indicates least heterogeneity, $30\% < I^2 < 50\%$ indicates moderate heterogeneity, $50\% < I^2 < 75\%$ indicates substantial heterogeneity, and $I^2 > 75\%$ indicates considerable heterogeneity.[10]

For the quality assessment of the included studies, the Newcastle–Ottawa Quality Assessment form was used for cohort and case-control studies. In contrast, the Cochrane Risk of Bias Tool was used for clinical trials. Two reviewers (JM and FH) averaged the scoring, with a third reviewer (GK) resolving any disagreements. Moreover, a table encompassing the included studies’ specific characteristics, such as the groups compared, fluid type, primary outcomes, clinical settings, and other relevant data, was included in the Supplemental Material.

To assess the potential for publication bias in our meta-analysis, we performed Egger’s regression test, which evaluates the funnel plot asymmetry by regressing the standard errors of the log-transformed odds ratios (log ORs) against the log ORs themselves.[11] For studies reporting medians instead of means, we applied the method described by Hozo *et al*, estimating the mean and standard deviation from the median, range, and size of the sample.[12] A significant regression intercept suggests the presence of publication bias. As for sensitivity analysis, a leave-one-out approach was adapted to evaluate the robustness of the meta-analysis results. For each outcome of interest, namely, the 90-day mortality rate and the 72-h intubation rate, the pooled OR and its 95% CIs were recalculated iteratively, each time excluding 1 study from the model. This analysis serves to identify any individual study that may disproportionately influence the meta-analysis summary effect, which was part of the Supplemental Material. For publication bias and sensitivity analysis, the statistical analyses were conducted using a custom Python script version 3.8 leveraging libraries such as NumPy for numerical computations and SciPy

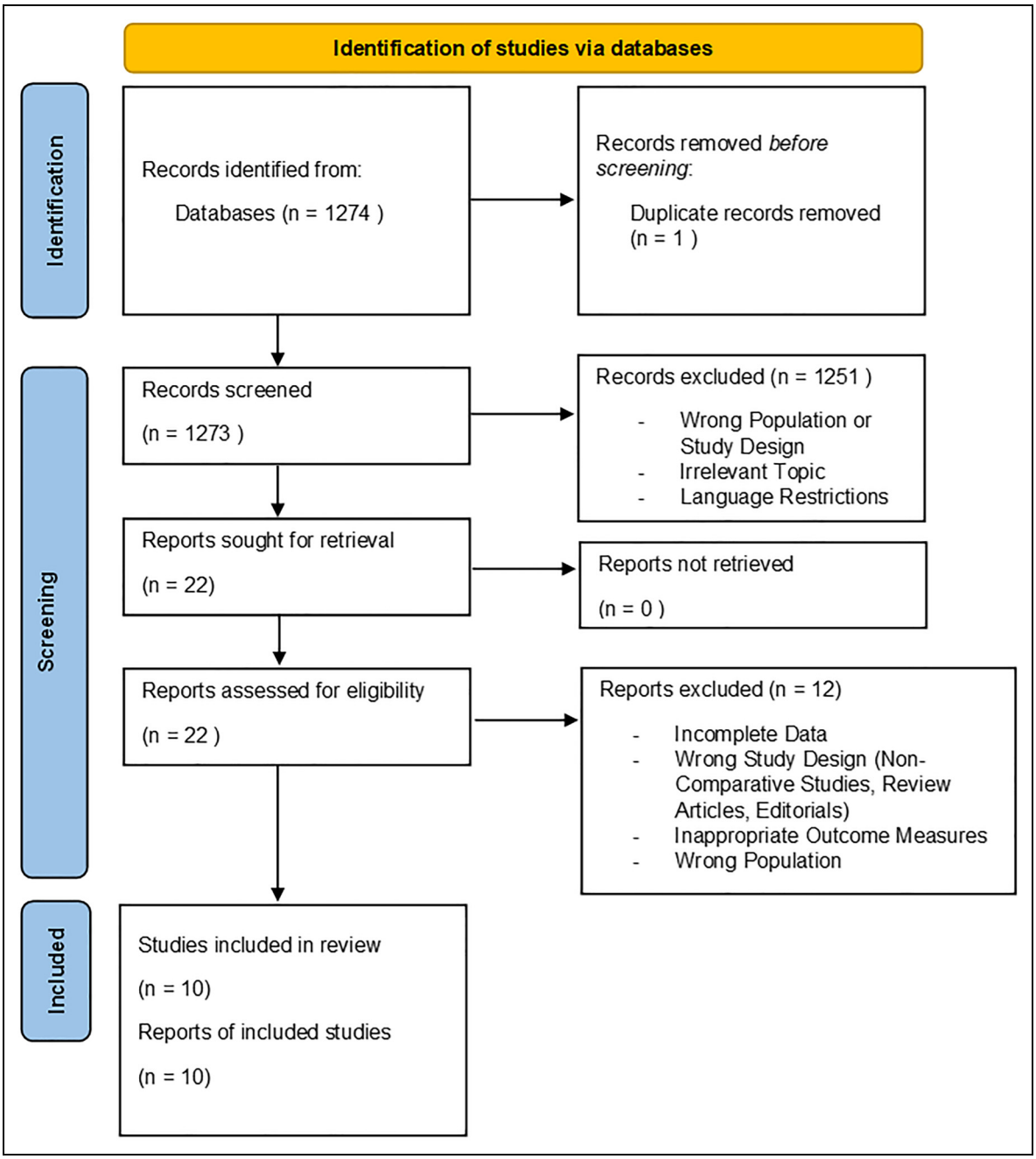

Figure 1. PRISMA flow diagram.

for statistical functions. Visual representations were created using the Matplotlib library.

Results

The search strategy identified 1274 studies. Of these, 1254 were excluded based on title and abstract. Of the remaining 22 studies, 12 were excluded after full-text review because of incomplete or overlapping data, and 10 were selected for analysis and review (Table 1 and Figure 1). The quality assessment of these studies revealed that the majority was of good quality, with most studies scoring above 5 on a 9-point scale, indicating a reliable level of robustness in their methodology and outcomes (Tables 2 and 3).

As for the characteristics of the included studies, they encompassed a range of clinical settings, primarily hospitalized patients in emergency departments and had both ICU and non-ICU patients. The types of fluid used for resuscitation were predominantly crystalloids. However, the studies did not compare the kind of crystalloids used for resuscitation, but it was mentioned that lactated Ringer (LR) was the most used type of fluid in some of the studies with no further details.

Table 1. Studies Investigating GDFR and Low-volume Fluid Resuscitation in ESRD Patients with Sepsis.

Study	Guideline-Directed Fluid Resuscitation	Low-volume Fluid Resuscitation	Total Patients
Boccio[5]	5	12	17
Rice[13]	55	51	106
Kuttab[14]	82	19	101
Lee[15]	214	115	329
Rajdev (2020)[16]	24	80	104
Rajdev (2021)[17]	53	51	104
Rosen[18]	71	43	114
Huebinger[19]	20	60	80
PETAL Clinical Trials Network[20]	40	33	73
Chernoby[21]	30	126	156

Table 2. Newcastle–Ottawa Scale Quality Ratings of the Included Studies.

Study Reference	Selection (4 Points Max)	Comparability (2 Points Max)	Outcome (3 Points Max)	Total Score (9 Points Max)
Lee (2017)	2	2	2	6
Rosen (2021)	2	1	1	5
Huebinger (2021)	3	2	2	7
Chernoby (2022)	2	2	3	7
Rajdev (2019)	3	2	2	7
Rajdev (2020)	3	1	2	6
Boccio (2021)	4	2	3	9
Rice (2020)	3	0	2	5
Kuttab (2019)	3	1	2	6

The primary outcomes focused on in-hospital mortality and intubation rates, with some studies also considering additional factors such as compliance with fluid resuscitation guidelines and the impact of other treatments like antibiotics and vasopressors.

Among these studies, 1184 patients were investigated, 593 of whom received GDFR of 30 cc/kg (Table 4). Our meta-analysis failed to prove any statistically significant difference in mortality (OR = 1.23; CI = 0.92-1.65; $I^2 = 0\%$) (Figure 2). All studies reported mortality rates ranging from 29% to 50% in the subset of ESRD patients with sepsis. The ORs of 90-day mortality of patients receiving GDFR versus low-volume resuscitation suggested higher mortality with the GDFR group. For instance, the studies by Boccio, Rosen, and the PETAL Clinical Trials Network reported ORs greater than 1 (2.00, 2.36, and 2.41, respectively). However, it is important to note that the CIs for these ORs are quite wide and cross 1.0, indicating a lack of statistical significance. According to Rice *et al*, a significant difference in length of stay was observed in patients with GDFR compared with those with the conservative approach. In contrast, Rajdev *et al*, in neither study, did not show any difference in length of stay between the compared groups. As for the intubation rate, 304 patients were investigated, with 102 receiving GDFR. There was no statistically significant difference between the 2 groups across the studies (Table 5). The related meta-analysis also failed to demonstrate any benefit in intubation rate (OR = 1.91; CI = 0.91-4.04; $I^2 = 0\%$) (Figure 3).

In assessing the potential for publication bias within the studies of 90-day mortality, Egger's test revealed a regression slope of −0.167 and an intercept of 0.813, with a correlation coefficient (R value) of −0.143. The P value associated with this test was .693, and the standard error of the regression was 0.409. These results suggest a lack of significant publication bias within the meta-analyzed studies (Figure 4). The Egger's test for the 72-h intubation rate revealed a regression slope of 1.734 and an intercept of −0.577, with a correlation coefficient (R value) of 0.564. The P value associated with this test was .436, and the standard error of the regression was 1.797. These findings indicate no statistically significant evidence of publication bias within the studies for the 72-h intubation rate outcome (Figure 5).

The sensitivity analysis for the 90-day mortality rate employing the leave-one-out approach showed ORs entirely

Table 3. Cochrane Risk of Bias Assessment for the Included Clinical Trials.

Study Reference	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
PETAL Clinical Trials Network (2023)	√	?	√	×	√	√	?

above 1.0 when individual studies were sequentially excluded, consistently suggesting higher mortality associated with GDFR. Notably, excluding studies such as Boccio (2021) and Chernoby (2022) from the meta-analysis altered the pooled OR to 1.401 (CI: 1.126-1.743) and 1.435 (CI: 1.141-1.805), respectively. The only exception was Rosen (2021), which indicates that this study balanced the overall pooled outcomes. Similarly, the sensitivity analysis for the 72-h intubation rate showed an increased intubation rate with GDFR when the Boccio *et al* study was excluded with an OR of 1.989 and CI of 1.019 and 3.883, which indicates that this study substantially dampens the overall meta-analytic result (Supplemental Material).

Discussion

In our meta-analysis, which consolidated data from 10 distinct studies and included a cohort of 1184 ESRD patients with sepsis, we observed no discernible difference in mortality outcomes when comparing those treated with GDFR targets versus those managed conservatively. Furthermore, when we scrutinized the intubation rates, a crucial metric given the concerns about volume overload and respiratory complications, our analysis, based on 304 patients from 4 of the included studies, found no significant variance between the fluid resuscitation strategies. Notably, this is the first meta-analysis and systematic review that addresses this important issue. The prevailing Surviving Sepsis Guidelines strongly advocate administering 30 mL/kg of crystalloid fluids in the setting of sepsis.[3] However, a significant gap remains in the literature regarding the appropriateness of this recommendation, specifically for ESRD patients. Remarkably, no adequately powered study has delved into the ramifications of GDFR within this cohort. Furthermore, a detailed subgroup analysis targeting ESRD patients is almost absent from the influential studies informing these guidelines. For instance, the work by Govero *et al* in their research signaled enhanced outcomes in terms of mortality, length of hospital stay, and intubation rates when comparing GDFR to a more restrictive regimen across a broad patient demographic.[22] Importantly, they matched for multiple comorbidities, including ESRD. However, a crucial caveat is the absence of a distinct subgroup analysis for ESRD patients. As such, while their findings might suggest potential benefits of the guideline approach for the general population, extrapolating these results directly to the ESRD cohort would be premature and possibly erroneous.

Consequently, multiple research teams aimed to demonstrate a marked distinction between the 2 approaches in this population, yet none could conclusively do so.[13,16,17,1920–21] Several factors might account for this. Primarily, there is a lack of focus on ESRD patients in several studies, as mentioned above. For instance, Khan *et al*, in their large study involving 208 septic patients at risk for fluid overload such as ESRD, cirrhotic, and heart failure patients, showed that both approaches in fluid management had similar outcomes; still, no subgroup analysis was conducted which makes any conclusion regarding ESRD patients difficult.[23] Nevertheless, Liu *et al* evaluated the effect of applying a sepsis bundle in their extensive study and divided their population into subgroups.[24] Their data indicated

Table 4. Odds Ratio of 90-day Mortality of GDFR versus Low-volume Resuscitation in ESRD Patients with Sepsis.

Study	90-day Mortality (OR)	Confidence Interval
Boccio[5]	2	0.22-18.33
Rice[13]	0.92	0.22-3.9
Kuttab[14]	1.29	0.39-4.33
Lee[15]	1	0.54-1.85
Rajdev (2020)[16]	1.13	0.45-2.86
Rajdev (2021)[17]	0.87	0.39-1.9
Rosen[18]	2.36	0.92-6.07
Huebinger[19]	1	0.35-2.89
PETAL Clinical Trials[20] Network	2.41	0.9-6.47
Chernoby[21]	1.2	0.52-2.75

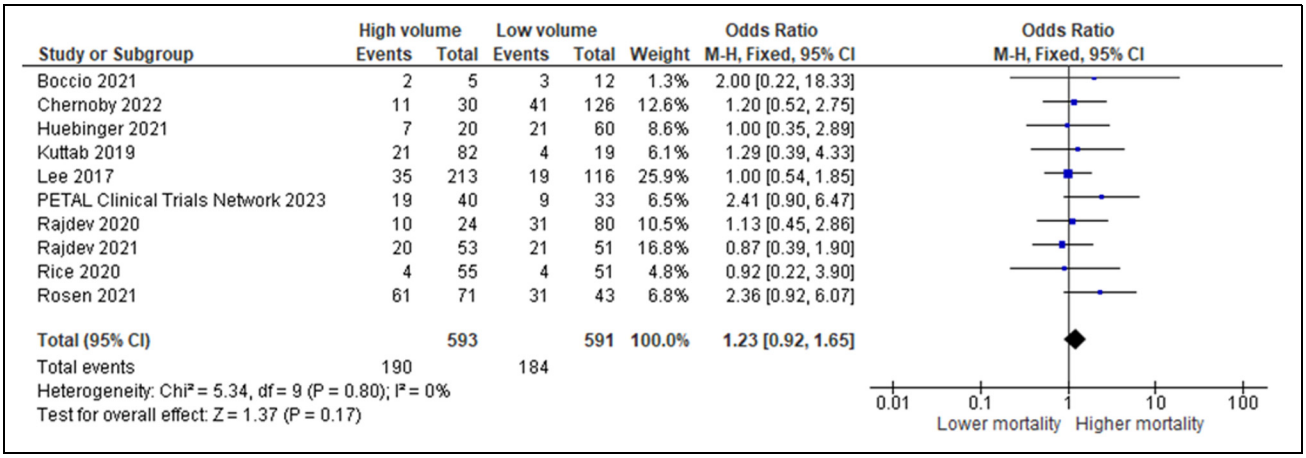

Figure 2. Forest plot showing the effect of high- versus low-volume resuscitation on 90-day mortality.

a marked correlation between enhanced fluid administration targets and improved mortality outcomes in patients with chronic kidney disease, especially when other factors like antibiotic timing remained constant across pre- and postbundle groups. However, the main drawback of this conclusion is that they combined chronic kidney disease and ESRD patients in the same group, making it hard to conclude ESRD patients.

Table 5. Odds Ratio of Intubation Rate within 72 h in High- versus Low-volume Resuscitation in ESRD Patients with Sepsis.

Study	72-h Intubation Rate (OR)	Confidence Interval
Boccio[5]	0.8	0.06-11.5
Rajdev (2020)[16]	2.7	0.56-13.09
Rajdev (2021)[17]	2.55	0.47-13.8
Huebinger[19]	1.69	0.59-4.85

Additional factors that prevent researchers from finding differences between both approaches include limited power and smaller sample sizes in individual studies.

Despite the absence of quality evidence in ESRD patients with sepsis, most societies still recommend the GDFR approach as it was successful in most studies in improving not only mortality and intubation rate but the length of stay, quality of life, rate of readmissions, and other endpoints that rarely evaluated in ESRD patients.[3,25,26] The decision to adopt GDFR is underpinned by years of evidence and a well-founded pathophysiological rationale.[3,2728–29] However, as Liu *et al* and many others mentioned, physicians still hesitate to follow it.[8,24,30] Support for GDFR is rooted in several fundamental physiological principles. Firstly, providing fluids rectifies volume deficits, ensuring that essential organs receive adequate blood flow, particularly during the widespread inflammation of sepsis.[31,32] By improving blood circulation, the reliance on less efficient

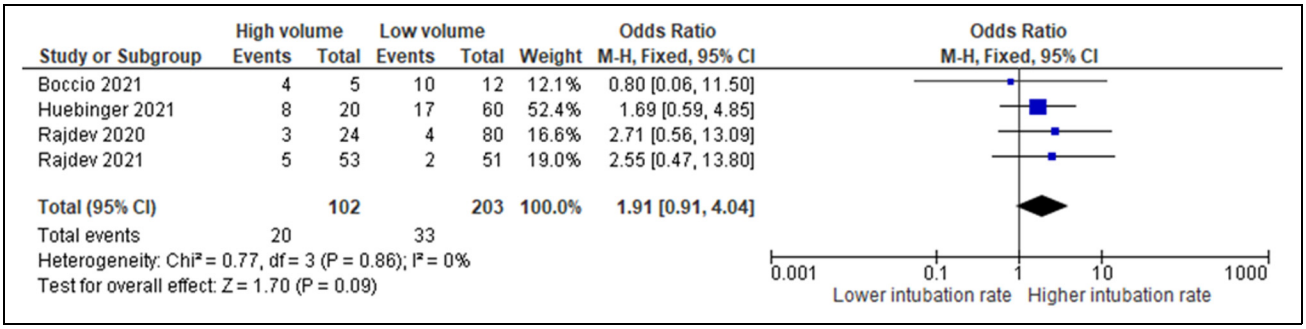
High volume
Low volume
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Boccio 2021 4 5 10 12 12.1% 0.80 [0.06, 11.50]
Huebinger 2021 8 20 17 60 52.4% 1.69 [0.59, 4.85]
Rajdev 2020 3 24 4 80 16.6% 2.71 [0.56, 13.09]
Rajdev 2021 5 53 2 51 19.0% 2.55 [0.47, 13.80]
Total (95% CI) 102 203 100.0% 1.91 [0.91, 4.04]
Total events 20 33
Heterogeneity: Chi² = 0.77, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)
0.001
0.1
1
10
1000
Lower intubation rate
Higher intubation rate

Figure 3. Forest plot showing the effect of high- versus low-volume resuscitation on intubation rate.

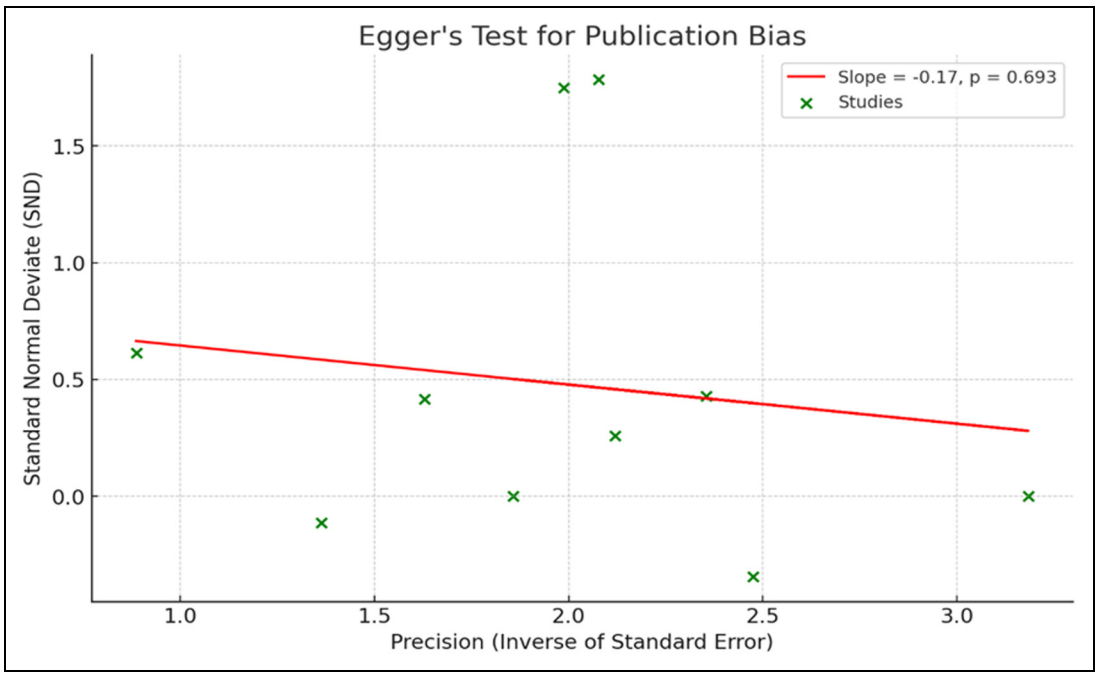

Figure 4. Scatter plot showing Egger's test for publication bias for the studies included to address 90-day mortality.

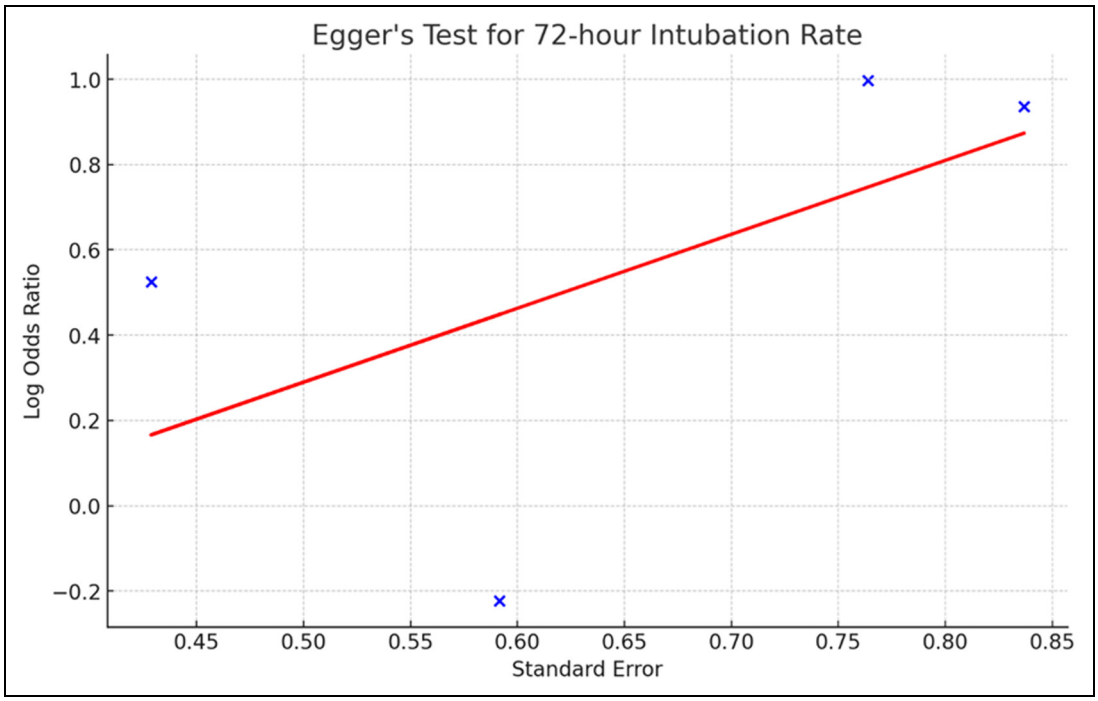

Figure 5. Scatter plot showing Egger's test for publication bias for the studies included to address the 72-h intubation rate.

anaerobic metabolic pathways decreases, diminishing acid buildup and potentially attenuating an escalating cytokine response that could culminate in a cytokine storm.[33,34] Secondly, maintaining an optimal fluid balance enhances cardiac performance. The Frank–Starling principle posits that the heart's stroke volume increases as the volume of blood filling the heart increases to a certain point. In sepsis, replenishing fluids ensures that the heart operates within an optimal range on this curve, aiding in counteracting sepsis-induced cardiac dysfunction.[31,32,35] Lastly, by increasing perfusion and possibly diluting inflammatory agents and toxins in the bloodstream, fluids can moderate the expression of leukocyte surface markers and decrease the rate of complications such as sepsis-induced cardiomyopathy or kidney injury, reinforcing the importance of GDFR.[1,35,36] Thus, some clinicians would interpret our nonstatistically significant findings as supporting evidence that GDFR is not linked to higher mortality and intubation rates in ESRD patients, which could encourage more physicians to adopt this approach. However, we advise caution when broadly applying the GDFR approach. The meta-analysis shows that while the pooled results do not present a statistically significant difference, individual studies strongly suggest that GDFR increases mortality risk in ESRD patients. This could lead to the conclusion that high-volume resuscitation might generally be harmful, supported by most individual study outcomes.

It is essential to note that most of the guidelines are built on studies done in resource-rich settings. Nonetheless, in contexts with limited medical resources, the well-known benefits of GDFR were not always replicated. Two prominent trials, the Simplified Severe Sepsis Protocol (SSSP) and its successor, SSSP-2, focused on early fluid management for adults with sepsis in environments without regular access to intensive care facilities or mechanical ventilation.[37,38] The SSSP trial in Zambia compared conventional care to a 6-h protocolized regimen involving early fluid boluses, vasopressors for mean arterial pressure (MAP) targets, and blood transfusions for hemoglobin targets. It was halted prematurely due to concerns of increased mortality among patients presenting with hypoxemic respiratory distress under protocolized care.[37] The subsequent SSSP-2 trial aimed to offset respiratory risks by excluding those with potential respiratory failure and incorporating safeguards against deteriorating respiratory function. Thus, with these adjustments, patients under the sepsis protocol received more intravenous fluids in the early phase and showcased greater serum lactate reduction.[38] Nevertheless, they faced a higher likelihood of respiratory deterioration and increased in-hospital mortality rates. The compromised outcomes from enhanced fluid administration in these studies might stem from the absence of mechanical ventilation, prevalent patient conditions like severe malnutrition and hypoalbuminemia, or complications from specific infections, such as malaria or tuberculosis.[39] Drawing insights from the studies in resource-constrained settings, the recent CLOVERS trial also presents a compelling challenge to the GDFR approach in resource-rich environments.[20] The CLOVERS trial critically examined the outcomes between a fluid restrictive strategy, emphasizing early vasopressor use, and a liberal fluid approach mirroring GDFR. Remarkably, primary results showed a non-statistically significant difference in mortality rates before 90-day discharge: 14.0% for the restrictive group and 14.9% for the liberal one, with an estimated difference of −0.9% (*P*

= 0.61). Furthermore, efficacy and safety metrics demonstrated no significant variations between the 2 strategies.[20]

The intricate results from the trials above underscore the complexity of fluid management in septic shock and emphasize that a uniform approach might not be universally effective. Careful attention is paramount, especially when extrapolating these findings to special patient populations like those with ESRD, as they are at higher risk of having pulmonary edema. The reason behind the potential increase in intubation and mortality manifests in the fact that ESRD patients exhibit a heightened susceptibility to chronic diseases, with malnutrition contributing to hypoalbuminemia and lower intravascular oncotic pressure. This, in turn, escalates the risk of interstitial edema, concomitant with the prevalent hyperchloremia in ESRD patients.[40] Moreover, the administration rate of resuscitation fluids and their composition can significantly impact the integrity of the endothelial glycocalyx. As highlighted in recent studies in pediatric and adult populations, aggressive fluid resuscitation has been associated with damage to the glycocalyx, which compounds vascular permeability issues and exacerbates inflammation.[4142–43] This is particularly pertinent in ESRD patients, where the delicate balance of fluid homeostasis is already compromised, and vascular instability is present. This interplay may result in ineffective resuscitation or even worsening the initial edematous presentation, especially with normal saline administration. Thus, it is imperative to consider that numerous previous investigations have discussed the potential harmful effects of normal saline with resuscitation. A meta-analysis encompassing 15 studies comparing balanced solutions such as LR to normal saline has deduced a diminished overall mortality, 28/30-day mortality in LR recipients.[44] This outcome can be attributed to the exacerbation of hyperchloremia observed in patients administered normal saline, wherein hyperchloremia is associated with deteriorating renal perfusion and metabolic acidosis.[45,46]

Given ESRD's distinct fluid balance challenges, precision medicine and modalities that accurately assess a patient's fluid responsiveness status could be invaluable. However, evidence remains ambiguous, with limited studies focusing on the ESRD cohort. One of the most used modalities is central venous pressure and parameter monitoring.[474849–50] Notably, a large meta-analysis found no difference in outcomes by comparing the 3 approaches: protocolized resuscitation steered by central venous pressure and oxygenation indicators, protocolized resuscitation without central venous oversight, and physician-driven care bypassing central venous monitoring.[51] However, Chen *et al* spotlighted the merits of central venous pressure measurement, showcasing a statistically significant improvement in septic shock mortality outcomes even when considering potential confounders.[52] The bedside point-of-care ultrasound (POCUS) is another modality that has been more commonly used and provides a less invasive option is the bedside point-of-care ultrasound (POCUS). POCUS can be used to gauge volume status and, more importantly, dynamic predictors for fluid responsiveness by assessing the internal jugular vein or inferior vena cava diameter and distensibility index. Also, it helps evaluate stroke volume variation, cardiac output, and arterial pulse pressure.[50,53] Although its efficacy remains conclusively established in the wider population, its use for ESRD patients can offer crucial insights into their unique fluid balance intricacies, thus ensuring that fluid resuscitation strategies are safe and effective. However, limitations of this technique include ultrasound availability, physician skills in ultrasonography, and poor echogenicity, particularly in mechanically ventilated patients.[54,55] Additionally, modalities such as pulmonary arterial catheterization (PAC) have been explored over the past few decades in assessing the fluid status of hospitalized patients.[5657–58] PAC provides precise cardiac output measurements and fluid responsiveness. However, its invasive nature poses a risk of potential complications leading to its abandonment by multiple institutions, and its efficacy in ESRD patients is not thoroughly evaluated.[59]

Despite the valuable insights drawn from our meta-analysis, there are inherent limitations. First and foremost, it was not possible to differentiate between sepsis and septic shock across the included studies, as they employed varying diagnostic criteria. Not all studies consistently documented key parameters such as lactate levels and MAP, which are crucial for distinguishing between these clinical entities. This variability in documentation and criteria inevitably added to the complexity of our analysis and interpretation of the results. Thus, another key limitation is the potential variability in treatment protocols across individual studies, such as the type of broad-spectrum antibiotics used and the order as well as the number of vasopressors used to maintain a MAP of $\geq$65 mm·Hg in patients who become hypotensive during or after initial fluid resuscitation. These components are essential in managing sepsis, and their omission from our analysis could influence our findings' interpretation. Furthermore, an I^2 of 0% does not definitively assert the absence of any heterogeneity but indicates that any differences in results among the included studies are not statistically significant. Additionally, when considering outcomes related to mechanical ventilation, our sample size was relatively modest, potentially limiting the power to detect significant differences between the fluid strategies. Moreover, while we evaluated the quantity of fluid resuscitation, the composition of the crystalloids (balanced vs unbalanced) was not analyzed, which could influence the outcomes due to different effects on acid–base balance and electrolyte levels. Lastly, our meta-analysis focused on short-term outcomes such as mortality and intubation rates, potentially overlooking long-term outcomes and quality of life post-treatment. As with all meta-analyses, our findings are limited by the quality and comprehensiveness of the studies included. Hence, future research with larger cohorts, clear differentiation between sepsis and septic shock, and more detailed analyses of ventilation outcomes will be instrumental in refining and confirming our observations.

Finally, our research findings indicate that administering GDFR to ESRD patients with sepsis does not lead to higher mortality or intubation rates. However, the study does not confirm any benefit with GDFR either. This suggests that clinicians may still follow the current guidelines without causing

any additional harm to the patients. However, while GDFR has physiological advantages, its universal applicability must be determined. Thus, we recommend that clinicians exercise caution, use personalized judgment, and integrate precision medicine into the decision-making process. They may also consider using old or new modalities to optimize fluid management, especially since our results indicated a potential increase in mortality rates. However, these results did not reach statistical significance. The current landscape reveals a sizable gap in research involving the growing ESRD population, underscoring the urgency for future investigations to center on this distinct subgroup.[60]

Author Contributions

SES conceptualized the study. GK and KEG designed the study. GK, NP, and JK developed the methodology and conducted the systematic search and screening of studies, with KEG resolving inclusion disagreements. VK, NP, and JK managed data curation. KEG registered the study. GK and KEG performed the statistical analysis. JM and FH assessed the quality of studies, with GK resolving any discrepancies. GK, KEG, NP. JK, SA, TR, and SAB drafted the initial manuscript, which was critically revised by MF, DE, MC, and HEH from a critical care perspective and SES from a nephrology perspective. SES supervised and administered the project.

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Supplemental Material

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References

1. van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol.* 2017;17(7):407-420.
2. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *Br Med J.* 2016;353(i1585):26–40.
3. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143.
4. Jones TW, Smith SE, Van Tuyl JS, Newsome AS. Sepsis with preexisting heart failure: management of confounding clinical features. *J Intensive Care Med*. 2021;36(9):989-1012.
5. Boccio E, Haimovich AD, Jacob V, Maciejewski KR, Wira CR, Belsky J. Sepsis fluid metric compliance and its impact on outcomes of patients with congestive heart failure, end-stage renal disease or obesity. *J Emerg Med*. 2021;61(5):466-480.
6. Trivedi V, Bavishi C, Jean R. Impact of obesity on sepsis mortality: a systematic review. *J Crit Care*. 2015;30(3):518-524.
7. Kooman JP, van der Sande FM. Body fluids in end-stage renal disease: statics and dynamics. *Blood Purif*. 2019;47(1-3):223-229.
8. Abou Dagher G, Harmouche E, Jabbour E, Bachir R, Zebian D, Bou Chebl R. Sepsis in hemodialysis patients. *BMC Emerg Med.* 2015;15(15):1-6.
9. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int*. 2000;58(4):1758-1764.
10. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
11. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J.* 1997;315(7109):629-634.
12. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol.* 2005;5(5):1-10.
13. Rice DM, Ratliff PD, Judd WR, Kseibi SA, Eberwein KA. Assessing the impact of CKD on outcomes in septic shock patients receiving standard vs reduced initial fluid volume. *Am J Emerg Med*. 2020;38(10):2147-2150.
14. Kuttab HI, Lykins JD, Hughes MD, et al. Evaluation and predictors of fluid resuscitation in patients with severe sepsis and septic shock. *Crit Care Med*. 2019;47(11):1582.
15. Lee JJ, Taylor SL, Adams JY. Fluid resuscitation and mortality in sepsis with end-stage renal disease. C23. Critical care: what can be measured can be improved-investigating the epidemiology and outcomes of patients with acute critical illness: American Thoracic Society; 2017. p. A5020.
16. Rajdev K, Leifer L, Sandhu G, et al. Fluid resuscitation in patients with end-stage renal disease on hemodialysis presenting with severe sepsis or septic shock: a case control study. *J Crit Care*. 2020;55(1):157-162.
17. Rajdev K, Leifer L, Sandhu G, et al. Aggressive versus conservative fluid resuscitation in septic hemodialysis patients. *Am J Emerg Med*. 2021;46(3):416-419.
18. Rosen D, Whelan K, Hao S, et al. Excess fluid resuscitation of septic patients with congestive heart failure or end stage renal disease may be associated with increased mortality. TP53. TP053 sepsis and multiorgan failure: American Thoracic Society; 2021. p. A2714.
19. Huebinger RM, Walia S, Yealy DM, Kellum JA, Huang DT, Wang HE. Outcomes of end-stage renal disease patients in the PROCESS trial. *J Am College Emerg Phys Open*. 2021;2(1): e12358.
20. National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network. Early restrictive or liberal fluid management for sepsis-induced hypotension. *N Engl J Med*. 2023;388(6):499-510.
21. Chernoby K, Dzingle A, Elefritz J, et al. 7: Impact of fluid resuscitation in end-stage renal disease patients with septic shock. *Crit Care Med*. 2022;50(1):4.
22. Govero AB, Yarrarapu SNS, Harrison MF, et al. Surviving sepsis guideline-directed fluid resuscitation: an assessment of practice patterns and impact on patient outcomes. *Critical Care Explorations*. 2022;4(7):25-49.
23. Khan RA, Khan NA, Bauer SR, et al. Association between volume of fluid resuscitation and intubation in high-risk patients with sepsis, heart failure, end-stage renal disease, and cirrhosis. *Chest*. 2020;157(2):286-292.

24. Liu VX, Morehouse JW, Marelich GP, et al. Multicenter implementation of a treatment bundle for patients with sepsis and intermediate lactate values. *Am J Respir Crit Care Med.* 2016; 193(11):1264-1270.
25. Egi M, Ogura H, Yatabe T, et al. The Japanese clinical practice guidelines for management of sepsis and septic shock 2020 (J-SSCG 2020). *J Intensive Care.* 2021;9(1):1-144.
26. Nguyen HB, Rivers EP, Abrahamian FM, et al. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. *Ann Emerg Med*. 2006;48(1):54.e1.
27. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Intensive Care Med*. 2018;44(1):925-928.
28. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2): 165-228.
29. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858-873.
30. Lowe KM, Heffner AC, Karvetski CH. Clinical factors and outcomes of dialysis-dependent end-stage renal disease patients with emergency department septic shock. *J Emerg Med*. 2018; 54(1):16-24.
31. Gordon D, Spiegel R. Fluid resuscitation: history, physiology, and modern fluid resuscitation strategies. *Emerg Med Clin*. 2020;38(4):783-793.
32. Byrne L, Van Haren F. Fluid resuscitation in human sepsis: time to rewrite history? *Ann Intensive Care.* 2017;7(2):1-8.
33. Wentowski C, Mewada N, Nielsen ND. Sepsis in 2018: a review. *Anaesth Intensive Care Med*. 2019;20(1):6-13.
34. Karbian N, Abutbul A, El-Amore R, et al. Apoptotic cell therapy for cytokine storm associated with acute severe sepsis. *Cell Death Dis.* 2020;11(7):535.
35. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. *Br J Anaesth.* 2016;116(3):339-349.
36. Jacobi J. The pathophysiology of sepsis—2021 update: part 1, immunology and coagulopathy leading to endothelial injury. *Am J Health-Syst Pharm.* 2022;79(5):329-337.
37. Andrews B, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Bernard GR. Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. *Crit Care Med*. 2014;42(11):2315-2324.
38. Andrews B, Semler MW, Muchemwa L, et al. Effect of an early resuscitation protocol on in-hospital mortality among adults with sepsis and hypotension: a randomized clinical trial. *JAMA*. 2017;318(13):1233-1240.
39. Brown RM, Semler MW. Fluid management in sepsis. *J Intensive Care Med*. 2019;34(5):364-373.
40. Wallia R, Greenberg A, Piraino B, Mitro R, Puschett JB. Serum electrolyte patterns in end-stage renal disease. *Am J Kidney Dis.* 1986;8(2):98-104.
41. Vincent JL, De Backer D, Wiedermann CJ. Fluid management in sepsis: the potential beneficial effects of albumin. *J Crit Care*. 2016;35(1):161-167.
42. Fernández-Sarmiento J, Lamprea S, Barrera S, et al. The association between prolonged capillary refill time and microcirculation changes in children with sepsis. *BMC Pediatr.* 2024;24(1):68.
43. Fernández-Sarmiento J, Salazar-Peláez LM, Acevedo L, et al. Endothelial and glycocalyx biomarkers in children with sepsis after one bolus of unbalanced or balanced crystalloids. *Pediatr Crit Care Med.* 2023;24(3):213-221.
44. Beran A, Altorok N, Srour O, et al. Balanced crystalloids versus normal saline in adults with sepsis: a comprehensive systematic review and meta-analysis. *J Clin Med.* 2022;11(7):1971.
45. Chang R, Holcomb JB. Choice of fluid therapy in the initial management of sepsis, severe sepsis, and septic shock. *Shock*. 2016;46(1):17-26.
46. Neyra JA, Canepa-Escaro F, Li X, et al. Association of hyperchloremia with hospital mortality in critically ill septic patients. *Crit Care Med*. 2015;43(9):1938-1944.
47. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8): 739-746.
48. Pope JV, Jones AE, Gaieski DF, et al. Multicenter study of central venous oxygen saturation (ScvO2) as a predictor of mortality in patients with sepsis. *Ann Emerg Med*. 2010;55(1):40-46.e1.
49. Boyd JH, Forbes J, Nakada T, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med*. 2011;39(2):259-265.
50. Chaudhuri D, Herritt B, Lewis K, et al. Dosing fluids in early septic shock. *Chest*. 2021;159(4):1493-1502.
51. Prism Investigators. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. *N Engl J Med*. 2017;376(23):2223-2234.
52. Chen H, Zhu Z, Zhao C, et al. Central venous pressure measurement is associated with improved outcomes in septic patients: an analysis of the MIMIC-III database. *Crit Care.* 2020;24(3): 1-10.
53. Mitchell OJ, Teran F, Patel S, Baston C. Critical care echocardiography: a primer for the nephrologist. *Adv Chronic Kidney Dis.* 2021;28(3):244-251.
54. Cortellaro F, Ferrari L, Molteni F, et al. Accuracy of point of care ultrasound to identify the source of infection in septic patients: a prospective study. *Intern Emerg Med.* 2017;12(1):371-378.
55. Integrated multiorgan bedside ultrasound for the diagnosis and management of sepsis and septic shock. Seminars in respiratory and critical care medicine: Thieme Medical Publishers, Inc. 333 Seventh Avenue, 18th Floor, New York, NY, 2021.
56. Yu DT, Platt R, Lanken PN, et al. Relationship of pulmonary artery catheter use to mortality and resource utilization in patients with severe sepsis. *Crit Care Med*. 2003;31(12):2734-2741.
57. Ganter MT, Alhashemi JA, Al-Shabasy AM, et al. Continuous cardiac output measurement by un-calibrated pulse wave analysis and pulmonary artery catheter in patients with septic shock. *J Clin Monit Comput*. 2016;30(2):13-22.
58. Cruz K, Franklin C. The pulmonary artery catheter: uses and controversies. *Crit Care Clin*. 2001;17(2):271-291.
59. Youssef N, Whitlock RP. The routine use of the pulmonary artery catheter should be abandoned. *Can J Cardiol*. 2017;33(1):135-141.
60. Filipska A, Bohdan B, Wieczorek PP, Hudz N. Chronic kidney disease and dialysis therapy: incidence and prevalence in the world. *Pharmacia*. 2021;68(2):463-470.